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Multiple retinal anomalies in schizophrenia

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ABSTRACT

Introduction: In addition to being a critical component of the visual system, the retina provides the opportunity for an accessible and noninvasive probe of brain pathology in neuropsychiatric disorders. Several studies have reported various retinal abnormalities in schizophrenia, some primary and others iatrogenic. There is now increasing evidence supporting the existence of retinal anomalies in schizophrenia across structural, neurochemical and physiological parameters. Here, we review the types of retinal pathology in schizophrenia and discuss how these findings may provide novel insights for future research into the neurodevelopmental neurobiology of this syndrome, and possibly as useful biomarkers.
Methods: Using the keywords schizophrenia, retina, pathology, electroretinogram (ERG), and/or optical coherence tomography (OCT) on PubMed, all studies using the English language within 30 years were reviewed. Methods were examined, and common themes were identified, tabulated, and discussed.
Results: We classified the reports of retinal pathology into primary and secondary. The major secondary retinal pathology is related to the iatrogenic effects of a once widely prescribed first generation antipsychotic (thioridazine), which was found to be associated with retinal pigment deposits, decreased visual acuity, and suppression of dark adapted ERG responses. The primary retinal findings were obtained via different measures primarily using ERG, OCT, and microvascular imaging. The most consistent findings were 1) decreased ERG wave amplitudes, 2) reduced macular volume, 3) thinning of retinal nerve fiber layer, and 4) widened venule caliber.
Conclusion: The abnormal pathobiological findings of the retina in schizophrenia may represent an important avenue for elucidating some of the neurodevelopmental aberrations in schizophrenia. The well replicated retinal anomalies could serve as biomarkers for schizophrenia and perhaps an endophenotype that may help identify at-risk individuals and to facilitate early intervention.

1. Introduction

Schizophrenia is a debilitating mental disorder with a prevalence of 0·5 to 1·5 worldwide in adults over 18, totaling over 50 million people worldwide (Nasrallah et al., 2011). It is characterized by fixed false beliefs (delusions), perceptual abnormalities (auditory, visual and other hallucinations), negative symptoms (apathy, alogia, emotional flattening, and social withdrawal) and cognitive deficits (especially memory and executive functions) (Nasrallah et al., 2011). Advances in neuroimaging and neurophysiology have provided opportunities to investigate aberrations in anatomy and neurophysiology in schizophrenia (Buckley, 2005). The retina, an embryonic extension of the brain, not only may be implicated in the pathophysiology of the visual disturbances, but may also provide the opportunity to establish an accessible and noninvasive probe of brain pathology in schizophrenia and related disorders (Schonfeldt-Lecuona et al., 2015; Meier et al., 2013; Gagné et al., 2015).

The human retina contains several layers of cells. The photoreceptors, rods for night (scotopic) vision and cones for day (photopic) vision, convert light into neural signals. These neural signals are transmitted through bipolar cells to the ganglion cells, the axons of which comprise the optic nerve and provide the final output from the retina. These vertical layers communicate via the horizontal and amacrine cells. The support cells in the retina are called Müller cells. Not only can the retina be studied structurally, using both optical coherence tomography (OCT) and retinal vessel imaging, but it can also be studied functionally, using the flash electroretinogram (ERG). Patients with schizophrenia do have known visual abnormalities, including decreased visual acuity, eye tracking dysfunction, decreased contrast sensitivity, and visual distortions (Gagné et al., 2015; Silverstein and Rosen, 2015; Viertiö et al., 2007). Though the ERG measures the functionality of the retina, correlations with visual changes is unknown at this time.

The ERG records a mass light-evoked electric potential from the retina in response to a light stimulus (Hébert and Lachapelle, 2003). It does so in one of two conditions: scotopic or photopic. In scotopic, or dark-adapted, conditions the patient dark adapted for at least 20 min (McCulloch et al., 2015). This allows for the assessment of rod or

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mixed rod-cone function (McCulloch et al., 2015). Photopic, or light adapted, conditions allow primarily for the assessment of cone function (McCulloch et al., 2015). ERG waveform has two major components shown in Fig. 1. The initial, negative deflection, the a-wave, represents the hyperpolarization of photoreceptors, and the positive b-wave represents Müller cell activity, possibly through a potassium mechanism, and depolarization of the bipolar cells (Meena et al., 2011). Oscillatory potentials are the low amplitude, high frequency wavelets present on the ascending part of the b-wave and are suspected to be generated by amacrine cells. The amplitudes of these waves, along with the implicit time (measured from stimulus to trough of the a-wave and peak of the b-wave), are most commonly used during analysis. Abnormalities in any of the previously discussed cells (photoreceptors, bipolar cells, and Müller cells) can be illustrated in changes to the ERG wave. In addition to being used clinically, in disorders like retinitis pigmentosa, the ERG is also used academically to provide data on the function of these cells in the retina (Kretschmann et al., 2000).

OCT is a recently developed, noninvasive imaging technique that can assess the Retinal Nerve Fiber Layer (RNFL) thickness, macular thickness, Macular Volume (MV), and foveal thickness (Ascaso et al., 2010). The macula, which contains the fovea and a high density of cone photoreceptors, is a specific pigmented area, near the center of the retina, that is responsible for central vision (Small, 1994). The RNFL is comprised of unmyelinated retinal cell axons, so thinning of this layer presumably reflects axonal loss (Schonfeldt-Lecuona et al., 2015; Lee et al., 2013). This has potential to mirror the documented loss in brain volume evidenced in several neuroimaging studies (Buckley, 2005). OCT has already proved useful for identifying thinning of RNFL in several neurodegenerative conditions, including multiple sclerosis and Alzheimer's disease, where RNFL thinning was correlated with the structural neurologic changes (Lee et al., 2013; Sergott et al., 2007; Lu et al., 2010; Parisi et al., 2001; Inzelberg et al., 2004; Double et al., 1996).

Schizophrenia is often associated with vascular disorders, but it is difficult to noninvasively assess the neural vasculature. Recent advances in retinal and fundal photography now allow for the assessment of retinal microvasculature as a proxy for cerebral vessels. Previous research has linked wider retinal venules to risk of stroke, dementia, and cerebrovascular disease and narrower retinal arterioles to hypertension (Meier et al., 2013). Other parameters, such as tortuosity, branching, and central light reflex, have been found to be associated with retinopathy and cardiovascular disease (Joshi, 2012; Brinchmann-Hansen et al., 1990). Cardiovascular disease is the most common cause of premature death in people with schizophrenia (Ohlsen, 2011; Colton and Manderscheid, 2006). This association cannot be solely due to risk factors, including antipsychotic side effects and lifestyle choices such as smoking, sedentary living and high-fat, high-calorie diet (Ohlsen, 2011). In a survey of eight states, it was found that public mental health patients had lost 13 to 30 potential years of life, depending on geography and year (Colton and Manderscheid, 2006). Other evidence for a vascular component involved in schizophrenia includes reduced cerebral blood flow, psychotic features in infections vascular disease (e.g. syphilis), and nail fold capillary bed abnormalities in patients with schizophrenia (Hanson and Gottesman, 2005). Cerebrovascular diseases have also been discussed as a feature of schizophrenia, with studies looking at antipsychotic usage as a risk factor (Meier et al., 2013). A recent study found a twofold increased risk of stroke in patients who used antipsychotic medications versus those who did not (Hsieh et al., 2015).

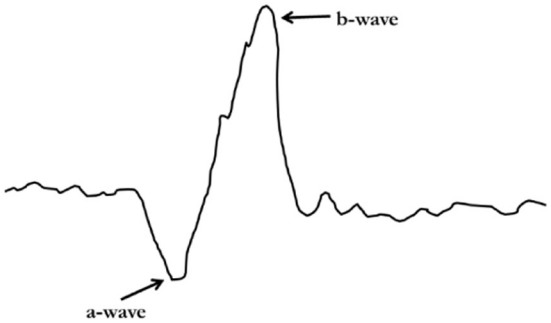

Fig. 1. Electroretinogram waveform illustrating the a-wave and b-wave.

Silverstein and Rosen recently published a review outlining visual processing impairments in schizophrenia (Silverstein and Rosen, 2015). They outlined the visual disturbances of patients and the factors, both retinal and other ocular dysfunctions, which could be contributing and the possibility of using retinal findings as biomarkers of pathology. Here, we will focus on retina, as an extension and proxy for the brain. We will describe the multiple retinal anomalies, both primary and secondary, and provide further insights into the possible neurobiological etiologies of schizophrenia. We will briefly discuss retinal anomalies in other psychiatric disorders. We will attempt to tie the hypothesized pathophysiology of schizophrenia to the retinal anomalies, and use this information discuss utilizing retinal pathologies as possible biomarkers that could provide novel avenues for future research.

2. Method

Using the keywords schizophrenia, retina, pathology, electroretinogram, and/or optical coherence tomography on PubMed, all studies using the English language within 30 years were reviewed. Methods were examined, and common themes were identified, tabulated, and discussed.

3. Results

A summary of all articles reviewed can be found in Table 1.

3.1. Schizophrenia

3.1.1. ERG

Several studies have demonstrated ERG abnormalities in schizophrenia, focusing primarily on a reduction in a- and b-wave amplitudes. A summary of these studies is shown below in Table 2. A pilot study used the ERG to measure retinal function as a marker for cell membrane omega-3 fatty acid depletion in schizophrenia (Warner et al., 1999). In addition to the findings shown below, they found no significant correlation between antipsychotic medication dose, in terms of chlorpromazine equivalents, and ERG recordings. While there were differences between the medicated patients and one unmedicated patient (illustrated in Fig. 2), ERG findings can be variable between individuals. A subsequent study found a significant reduction in a-wave amplitude ($p = 0{\cdot}0001$) in schizophrenia patients compared to the control and bipolar disorder groups at a baseline assessment, which was at least two weeks after they began receiving stable antipsychotic medications (Balogh et al., 2008). However, after eight continued weeks of treatment, this difference disappeared and there was reduction in psychotic symptoms, as evidenced by a reduction in PANSS scores. This study did not find a significant difference in a-wave latency or b-wave amplitude between the three groups. Of note, no dark adapted ERG was used in this group. They did not find any correlation between duration of treatment or the chlorpromazine-equivalent dose of antipsychotic medication, which both the schizophrenia and bipolar disorder groups were currently being treated with, and ERG findings. These findings were again confirmed by the largest ERG study to date ($N = 105$), which also identified novel anomalies (Hebert et al., 2015). They assessed b-wave implicit time, for the first time, which was found to be statistically and significantly increased. While Balogh et al. found reductions in symptoms and ERG changes after treatment, this study contained patients who were not refractory to treatment and still presented with

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